NDAs 19-030/S-009 & S-011
19-033/S-006

AUG 2 6 1999

Abbott Laboratories
Attention: Jessie Y. Lee, Ph.D.
200 Abbott Park Road
D-389, Building AP30
Abbott Park, IL 60064-3537

Dear Dr. Lee:

Please refer to your supplemental new drug applications dated June 26, 1998 (NDAs 19-030/S-009 and 19-033/S-006) and November 30, 1998 (NDA 19-030/S-011) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bretylium Toslyate Injection in Plastic Vials, 50 mg/mL (NDA 19-030) and Bretylium Tosylate Syringes and Ampul, 50mg/mL (NDA 19-033).

We acknowledge receipt of your submissions dated May 7, June 25 and July 6, 1999 (NDA 19-030/S-011) and December 3, 1999, February 26 and April 16, 1999 (NDAs 19-030/S-009 and 19-033/S-006).

The supplemental new drug applications 19-030/S-009 and 19-033/S-006 provide for draft labeling with the addition of a "Geriatric Use" subsection.

The supplemental new drug application 19-030/S-011 provides for draft labeling that combines the labeling of NDAs 19-030 and 19-033 and addition of the Aluer Plastic Vial.

The revisions are as follows:

NDAs 19-030/S-009 and S-011; and NDA 19-033/S-006

1. Under the **WARNINGS**/Hypotension subsection, the following paragraph has been added:

> Patients over 65 years may be at increased risk of developing orthostatic hypotension, especially when the recommended rate of intravenous infusion is exceeded. See **DOSAGE AND ADMINISTRATION**.

2. Under **PRECAUTIONS**, the following subsection has been added:

> Geriatric Use: Clinical studies of bretylium tosylate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or drug therapy.

Intravenous infusion, especially if administered at a rate beyond that recommended in the **DOSAGE AND ADMINISTRATION** section, may produce an increased risk of orthostatic hypotension in the elderly. See **WARNINGS**.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function, See **CLINICAL PHARMACOLOGY.**

3. Under the **DOSAGE AND ADMINISTRATION**/subsections A and B, the following sentence has been changed from:

More rapid infusion may cause nausea and vomiting.

to:

More rapid infusion may cause nausea and vomiting, and in patients older than 65 years, may increase the risk of developing orthostatic hypotension.

4. Throughout the labeling, “Bretylium Tosylate Injection” has been changed to, “Bretylium Tosylate Injection, USP.”

NDA 19-030/S-011

The heading has been changed from:

BRETYLIUM TOSYLATE
Injection,
AQUEOUS SOLUTION FOR THE ACUTE MANAGEMENT OF CARDIAC ARRHYTHMIAS
Plastic Vial
FOR INTRAMUSCULAR OR INTRAVENOUS USE ONLY

to:

BRETYLIUM TOSYLATE
Injection USP
AQUEOUS SOLUTION FOR THE ACUTE MANAGEMENT OF CARDIAC ARRHYTHMIAS
Abboject® Syringe
Ampul
Ansyr™ Plastic Syringe
Plastic Vial
Aluer™ Plastic Vial
FOR INTRAMUSCULAR OR INTRAVENOUS USE ONLY

2. Under the **DESCRIPTION** section, the third sentence of the second paragraph has been changed from:

> pH is 5.5 (3.5 to 7.0) for the Abboject® syringe, pH is 6.0 (3.5 to 7.) for the ampul.

to:

> pH is 5.5 (3.5 to 7.0) for the Abboject® syringe and AnsyrTM plastic syringe. pH is 6.0 (3.5 to 7.) for the ampul and plastic vial.

3. Under **HOW SUPPLIED**, the information on the containers has been changed from:

> Bretylium Tosylate Injection is supplied in 10 mL single-dose plastic Fliptop (List No. 9268).

to:

> Bretylium Tosylate Injection, USP is supplied in 10 mL single-dose Abboject Unit of Use Syringe (List NO. 9267), 10 mL single-dose ampuls (List No. 9263), 10 mL Ansyr plastic syringe (List No. 1698), 10 mL Aluer Plastic Vial (List No. 9268) and 10 mL single dose plastic Fliptop (List No. 9268).

4. The sentence, "Caution: Federal (USA) law prohibits dispensing without prescription." has been removed from the labeling.

5. All wording that was singular to a particular dosage form has been combined in this labeling.

Carton Label

The new carton label for the Aluer Vials is as follows:

10 mL Single-dose 5 Aluer™ Vials NDA 0074-9268-70
BRETYLIUM TOSYLATE Injection USP
500 mg (50 mg/mL)
Rx Only

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Each mL contains bretylium tosylate 50 mg. May contain hydrochloric acid and sodium hydroxide for pH adjustment. 0.241 mOsmol/mL (calc.) pH 6.0 (3.5 to 7.0).

For I.M. or I.V. use. Usual dosage: See insert. Use only if clear. Contains no bacteriostat: Use promptly and discard unused portion. Sterile, nonpyrogenic.
Tamper evident: Do not use vial if flexible cap is missing or if tabbed edge at base of cap is visible.
USE ASEPTIC TECHNIQUE
Vial access port is sterile when cap is intact. Alcohol swabbing is not required.

Do not access vial with needle. Use luer lock or slip luer syringe.
1. Twist and pull off cap.
2. Draw back syringe plunger to desired volume. Attach male end of syringe to female end of vial. To secure-push and twist until tight for luer lock syringe, or push all the way in for slip luer syringe.

3. Inject air into vial. With vial upside down and syringe attached, withdraw desired volume (if necessary, intermittently inject air into vial while withdrawing desired volume).

4. Return vial to upright position and disconnect syringe. Store at controlled room temperature 15° to 30°C (59° to 86°F).

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental applications are approved effective on the date of this letter.

1. The Heading should be changed to read as follows:

BRETYLIUM TOSYLATE
Injection USP
AQUEOUS SOLUTION FOR THE ACUTE MANAGEMENT OF CARDIAC ARRHYTHMIAS
Abboject® Syringe
Ansyr™ Plastic Syringe
Ampul
Plastic Fliptop Vial
Aluer™ Plastic Vial
FOR INTRAMUSCULAR OR INTRAVENOUS USE ONLY

2. The **HOW SUPPLIED** section should be changed to read as follows:

Bretylium Tosylate Injection is supplied in the following:

List No.	Container	Size
9267	Abboject Unit of Use Syringe	10 mL
1698	Ansyr Plastic Syringe	10 mL
9263	Single Dose Ampuls	10 mL
9268	Single Dose Plastic Fliptop Vial	10 mL
9268	Aluer Plastic Vial	10 mL

Store at controlled room temperature 15° to 30°C (59° to 86°F).

The final printed labeling (FPL) must be identical, to (and include the minor editorial revisions indicated above) the draft labeling included in your February 26, 1999 submissions (NDAs 19-030/S-009 and 19-033/S-006) and draft labeling included in your May 7, 1999 submission (NDA 19-030/S-011).

These revisions are the terms of the approval. Marketing the products before making the revisions, exactly as requested in the products' final printed labeling (FPL) may render the products misbranded and unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 19-030/S-009 and S-011 and 19-033/S-006. Approval of these submissions by FDA is not required before the labeling is used.

If you have any questions, please contact:

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(301) 594-5311

Sincerely yours,

Raymond J. Lipicky
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research